PATENT COOPERATION TREATY
EUROPEAN PATENT OFFICE

In re PCT APPLICATION of	
GILEAD SCIENCES, INC. et al.	Agent's File Ref. 588.F
International Application No. : PCT/US2004/043969	
International Filing Date: 29 December 2004	
For: PHOSPHONATES, MONOPHOSPHONAMIDATES, BISPHOSPHONAMIDATES FOR THE TREATMENT OF VIRAL DISEASES	

International Preliminary Examining Authority
European Patent Office
Erhardtstrasse 27
D-80298 Munich
Germany

RESPONSE TO WRITTEN OPINION OF THE ISA

Dear Sir:

This is responsive to the International Search Report and Written Opinion of the ISA, mailed May 19, 2005. These amendments will place this case into improved condition for proceedings under the Demand (filed of even date), and subsequent national or regional phase prosecution.

Referring to the Written Opinion, item V requires attention first off. As the ISA correctly points out, the compound claims in fact do cover a number of known compounds. In addition to the citations brought by the ISA, the examiner's attention is drawn to US Patent 5,798,340 and WO96/33200 (copies enclosed). These disclosures are concerned with various methoxyphosphonate antiviral purine analogues having substitutions at the purine N6, and/or substitution at the phosphonate hydroxyl group(s) by esters and amino acids. The examiner is invited to consider these references together with the references already of record.

This application is principally concerned with improved compositions for the treatment of HPV and carcinomas, particularly topical treatments. The Written

Opinion correctly points out that the focal antiviral compound PME-N6-(cyclopropyl)DAP ("cprPMEDAP") was known prior to applicants' work, and that claim 1 covered this compound. This was an oversight that obscured the nature of the invention, which is to provide a cprPMEDAP *analogue* which exerts particularly potent activity against HPV and carcinomas. While amidate prodrugs of various methoxyphosphonate antiviral compounds are known, it was not appreciated that such prodrugs would be particularly efficacious against HPV or carcinomas. As noted in the specification, pages 116 – 120, the mono- or diamidate prodrugs were considerably more effective against the targets than cprPMEDAP or conventional therapeutic controls. If anything at all could have been expected, it would have been that the parental drugs cprPMEDAP or PMEG (i.e., the antivirally active metabolites) would have been the more potent candidates. The data shows exactly the contrary. As seen in Table 79-2, for example, amidate prodrugs typically are well more than an order of magnitude more potent than the underlying parental drugs. The increased potency did not come at the expense of selectivity either, as can be appreciated from Tables 79-2 and 79-3.

Thus, the key feature of this invention is the identification of the cprPMEDAP amidate prodrugs for their highly desirable anti-HPV and anti-proliferative effect. The claims have been amended to reflect this. Thus, claim 1 has been amended so that the N6 position is substituted with hydrogen (one site) and W5 (the other site). The basis for this amendment includes original claims 2 and 4. This excludes from the scope of the claim the other PME analogues of the prior art.

Amended claim 1 now also specifies that at least one of the Y groups is an amidate. The basis for this amendment includes original claim 19. All of the claimed compounds are now amidates, consistent with the specification showings of substantially higher potency and selectivity for this class of compounds.

The examiner is requested to reconsider his position on novelty and inventive step, particularly as the claim scope now is commensurate with the search. Applicants apologize for any difficulties the initial claim scope may have caused.

Several further objections were raised. First, the relevant background art was not mentioned in the description. This has been remedied by the amendment to specification page 4 to recite D1-D4 as well as the two references newly cited above.

The second objection was to the language "used as". This has been remedied in the fashion suggested by the examiner.

New claims 57-59 are directed to a species of the invention, its formulation and use. Claim 57 is based on original claims 41 and 45, claim 58 is based on original claims 52-53 and claim 59 is based on original claims 119-121.

Specification page 27 was found to contain typographical errors (duplication of lines 9-11 and a typo for phenylalanine evident from the accompanying structure). These have been corrected in the amended page 27 submitted herewith.

This application is now believed to be ready for further action pursuant to the Demand.

Should the examiner wish to discuss this case further, he is invited to contact the undersigned.

Respectfully submitted,

James J. Wong

James J. Wong, J.D.
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Phone: (650) 522-5823
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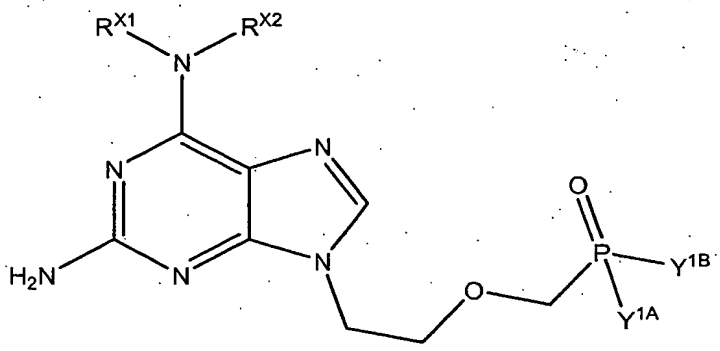
Attachments: Amended Claim Set; Amended Specification Pages 4 and 27
U.S. Patent 5,798,340; WO 96/33200 *(copies of patent references are not being sent by fax—hard copies only being sent with original confirmation documents by Federal Express Courier Service)*

What Is Claimed:

1. A compound of Formula I,



I

wherein:

Y^{1A} and Y^{1B} are independently Y^1;

R^{X1} is H and R^{X2} is W^5;

Y^1 is =O, -O(R^X), =S, -N(R^X), -N(O)(R^X), -N(OR^X), -N(O)(OR^X), or -N(N(R^X)(R^X)) provided that at least one Y^1 is –N(R^X);

R^X is independently R^1, R^2, R^4, W^3, or a protecting group;

R^1 is independently -H or alkyl of 1 to 18 carbon atoms;

R^2 is independently R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is -H, -F, -Cl, -Br, -I, $-CF_3$, -CN, N_3, $-NO_2$, or –OR^4;

R^{3b} is =O, -O(R^4), =S, -N(R^4), -N(O)(R^4), -N(OR^4), -N(O)(OR^4), or -N(N(R^4)(R^4));

R^{3c} is –R^4, -N(R^4)(R^4), -SR^4, -S(O)R^4, -S(O)$_2R^4$, -S(O)(OR^4), -S(O)$_2$(OR^4), -OC(R^{3b})R^4, -OC(R^{3b})OR^4, -OC(R^{3b})(N(R^4)(R^4)), -SC(R^{3b})R^4, -SC(R^{3b})OR^4, -

$SC(R^{3b})(N(R^4)(R^4))$, $-N(R^4)C(R^{3b})R^4$, $-N(R^4)C(R^{3b})OR^4$, $-N(R^4)C(R^{3b})(N(R^4)(R^4))$, W^3 or $-R^5W^3$;

R^{3d} is $-C(R^{3b})R^4$, $-C(R^{3b})OR^4$, $-C(R^{3b})W^3$, $-C(R^{3b})OW^3$ or $-C(R^{3b})(N(R^4)(R^4))$;

R^4 is -H, or an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2 to 18 carbon atoms;

W^3 is W^4 or W^5;

W^4 is R^6, $-C(R^{3b})R^6$, $-C(R^{3b})W^5$, $-SO_{M2}R^6$, or $-SO_{M2}W^5$, wherein R^6 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups; and

M2 is 0, 1 or 2;

and pharmaceutically acceptable salts thereof.

2. The compound of claim 1 wherein Y^{1A} and Y^{1B} are $-N(R^X)$.

3. The compound of claim 2 wherein R^X is R^2.

4. The compound of claim 3 wherein R^2 is R^4 substituted with R^{3d}.

5. The compound of claim 4 wherein R^4 is ethyl substituted with R^{3d}.

6. The compound of claim 5 wherein R^{3d} is $-C(R^{3b})OR^4$.

7. The compound of claim 6 wherein R^{3b} is =O.

8. The compound of claim 7 wherein R^4 is alkyl of 1 to 18 carbon atoms.

9. The compound of claim 1 wherein R^{3d} is $-C(R^{3b})OW^3$.

10. The compound of claim 1 wherein R^4 is propyl substituted with R^{3d}.

11. The compound of claim 1 wherein R^{3d} is $-C(R^{3b})OR^4$.

12. The compound of claim 3 wherein R^2 is R^4 independently substituted with two R^3 groups.

13. The compound of claim 12 wherein R^4 is methyl substituted with two R^3 groups.

14. The compound of claim 13 wherein one R^3 group is R^{3c}.

15. The compound of claim 1 wherein R^5 is methylene.

16. The compound of claim 1 wherein W^3 is W^5.

17. The compound of claim 14 wherein one R^3 group is R^{3d}.

18. The compound of claim 1 wherein R^{3c} is W^3.

19. The compound of claim 1 wherein Y^{1A} is $-N(R^X)$ and W^5 is a carbocycle.

20. The compound of claim 1 wherein Y^{1B} is $-N(R^X)$.

21. The compound of claim 1 wherein R^{3c} is $-R^5W^3$.

22. The compound of claim 16 wherein W^5 is a carbocycle.

23. The compound of claim 1 wherein Y^{1B} is $-O(R^X)$.

24. The compound of claim 23 wherein Y^{1B} is $-O(W^3)$.

25. The compound of claim 22 wherein said carbocycle is phenyl.

26. The compound of claim 1 wherein R^2 is R^4 substituted with R^{3c} and R^{3d}.

27. The compound of claim 26 wherein R^4 is ethyl substituted with R^{3c} and R^{3d}.

28. The compound of claim 1 wherein Y^{1A} and Y^{1B} are $-O(R^X)$.

29. The compound of claim 1 wherein R^{X2} is R^4.

30. The compound of claim 1 wherein R^2 is R^4 substituted with one R^3.

31. The compound of claim 30 wherein R^4 is methyl substituted with one R^3.

32. The compound of claim 31 wherein R^3 is R^{3a}.

33. The compound of claim 32 wherein R^{3a} is $-CF_3$.

34. The compound of claim 30 wherein R^4 is $-CH_2$-CF_3.

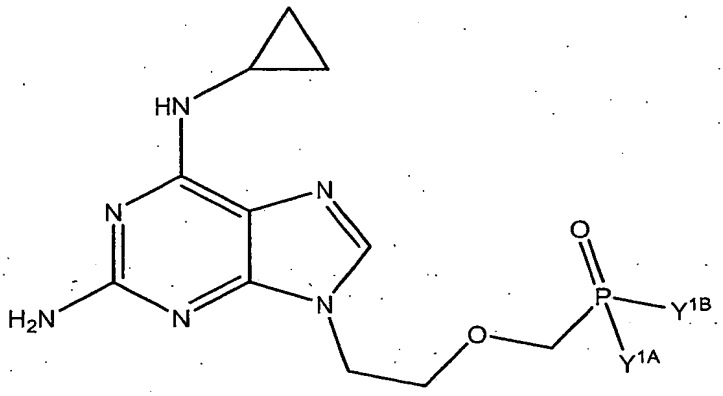
35. The compound of claim 1 for use as an antiproliferative agent.

36. The compound of claim 1 for use as an apoptotic agent.

37. The compound of claim 1 for use as an anti-HPV agent.

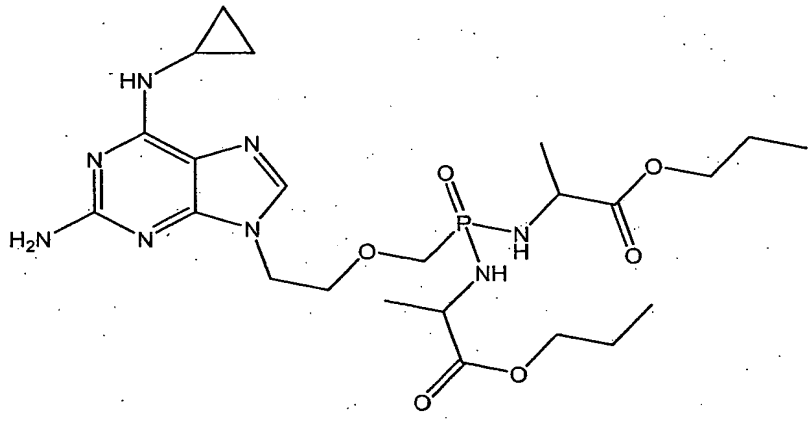
38. The compound of claim 1 for use as a topical anti-HPV agent.

39. The compound of claim 1 of the Formula IA,

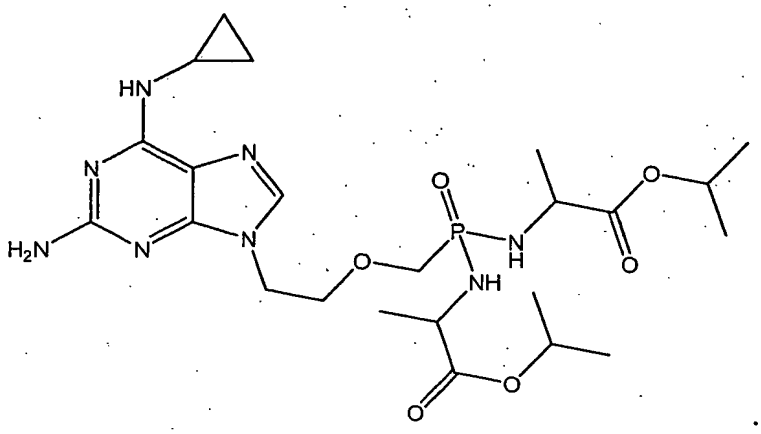


IA

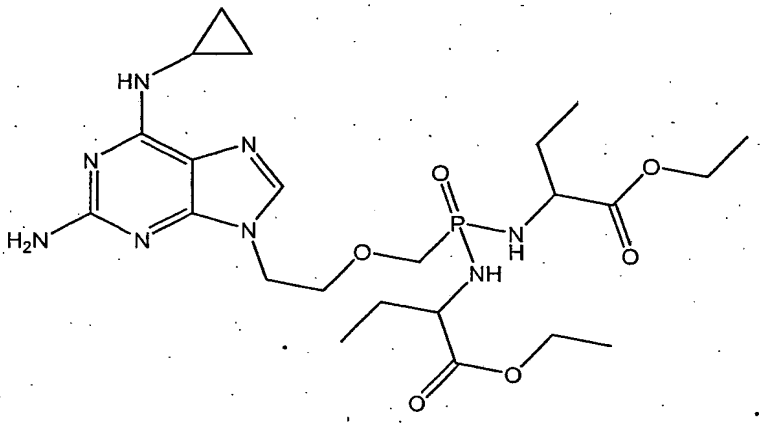
40. The compound of claim 1 of the formula,



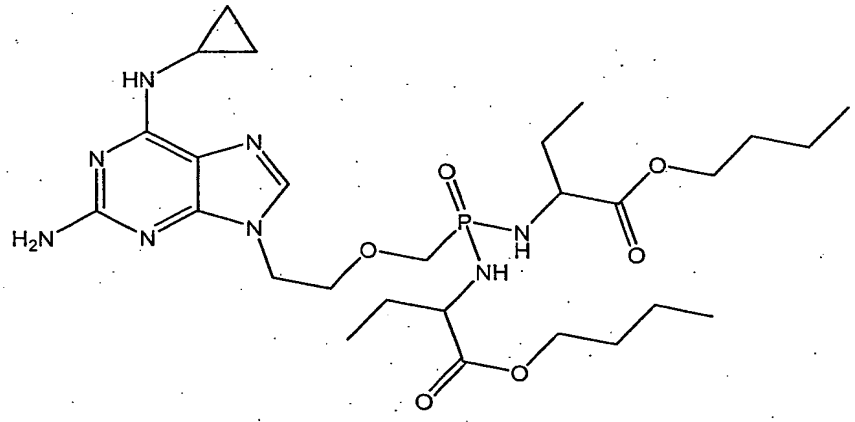
41. The compound of claim 1 of the formula,



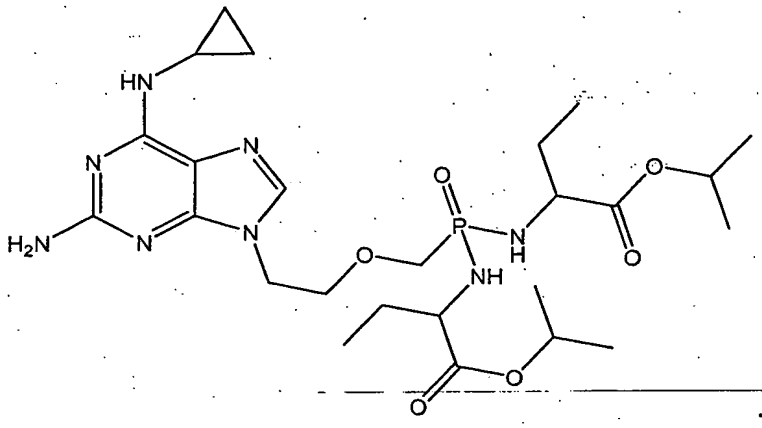
42. The compound of claim 1 of the formula,



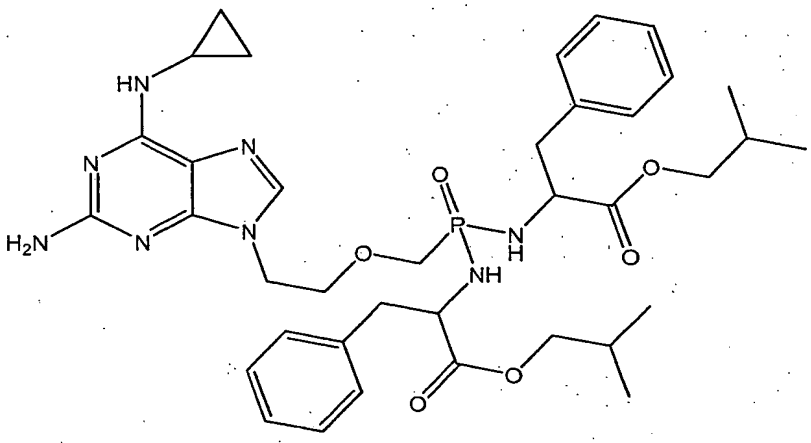
43. The compound of claim 1 of the formula,



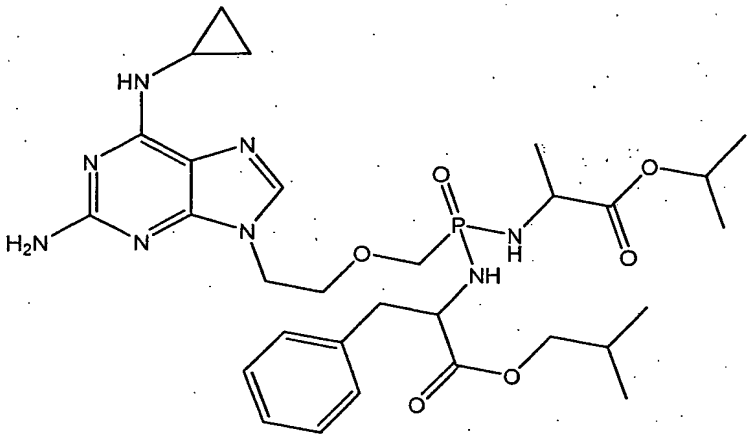
44. The compound of claim 1 of the formula,



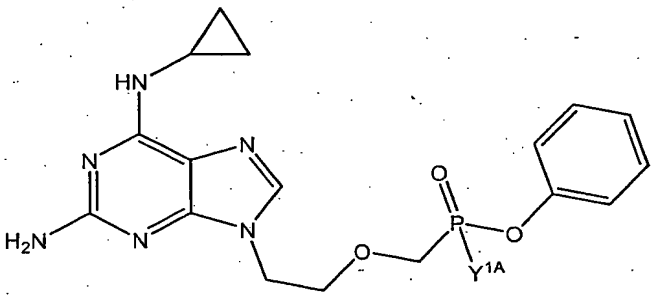
45. The compound of claim 1 of the formula,



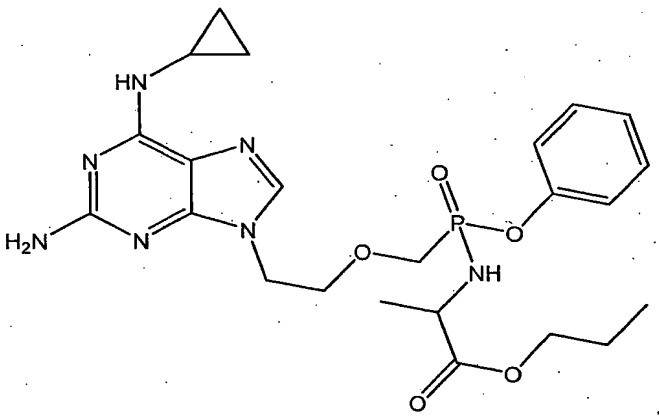
46. The compound of claim 1 of the formula,



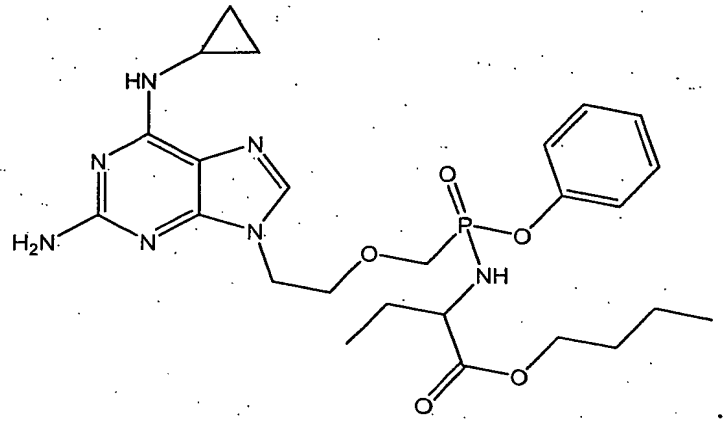
47. The compound of claim 1 of the formula,



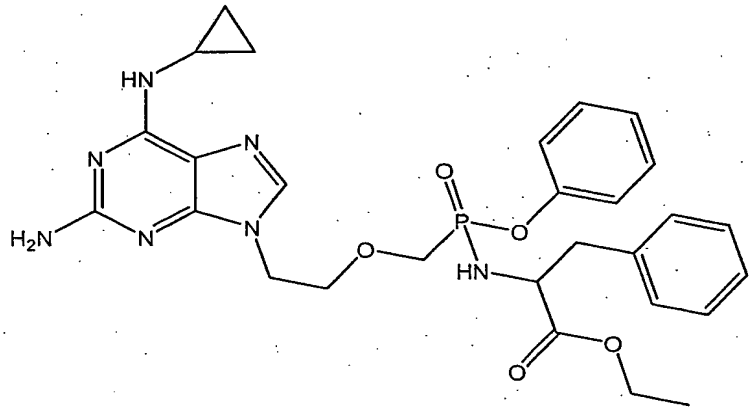
48. The compound of claim 1 of the formula,



49. The compound of claim 1 of the formula,



50. The compound of claim 1 of the formula,



51. A pharmaceutical composition comprising an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

52. The pharmaceutical composition of claim 51 where said composition is a gel composition.

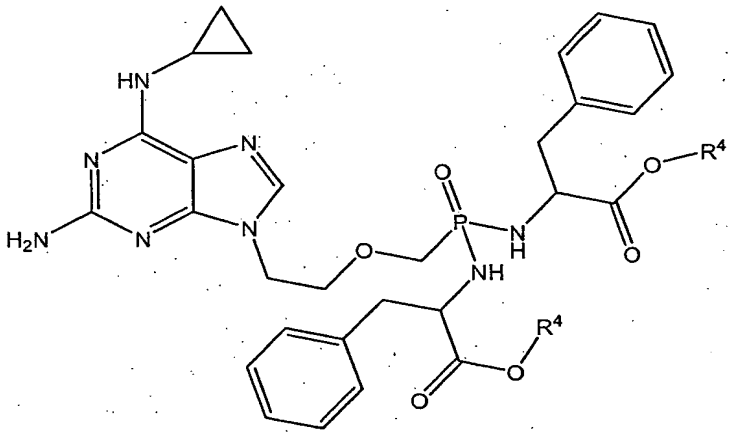
53. The pharmaceutical composition of claim 51, where said composition is an ointment composition.

54. A pharmaceutical composition comprising an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, and an effective amount of at least one antiviral agent, and a pharmaceutically acceptable carrier.

55. The pharmaceutical composition of claim 54, where said composition is a gel composition.

56. The pharmaceutical composition of claim 54, where said composition is an ointment composition.

57. A compound of the formula,



wherein R^4 is H, or an alkyl of 1 to 18 atoms, alkenyl of 2 to 18 carbon atoms or alkynyl of 2 to 18 carbon atoms and pharmaceutically acceptable salts thereof.

58. A gel or ointment comprising the compound of claim 57.

59. The ointment or gel of claim 58 for use as an antiproliferative, apoptotic or anti-HPV agent.

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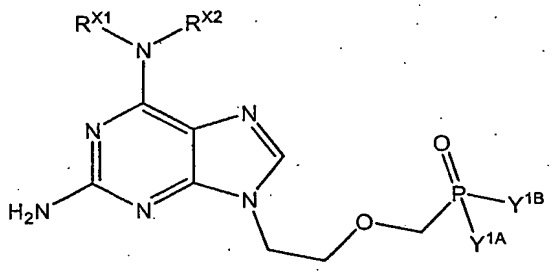
ABSTRACT OF THE DISCLOSURE

Compounds and compositions of Formula I are described, useful as anti-proliferative agents, and in particular anti-HPV,



I

wherein:

Y^{1A} and Y^{1B} are independently Y^1;

R^{X1} and R^{X2} are independently R^X;

Y^1 is =O, -O(R^X), =S, -N(R^X), -N(O)(R^X), -N(OR^X), -N(O)(OR^X), or -N(N(R^X)(R^X));

R^X is independently R^1, R^2, R^4, W^3, or a protecting group;

R^1 is independently -H or alkyl of 1 to 18 carbon atoms;

R^2 is independently R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is -H, -F, -Cl, -Br, -I, $-CF_3$, -CN, N_3, $-NO_2$, or $-OR^4$;

R^{3b} is =O, -O(R^4), =S, -N(R^4), -N(O)(R^4), -N(OR^4), -N(O)(OR^4), or -N(N(R^4)(R^4));

R^{3c} is $-R^4$, -N(R^4)(R^4), -SR^4, -S(O)R^4, -$S(O)_2R^4$, -S(O)(OR^4), -$S(O)_2$(OR^4), -OC(R^{3b})R^4, -OC(R^{3b})OR^4, -OC(R^{3b})(N(R^4)(R^4)), -SC(R^{3b})R^4, -SC(R^{3b})OR^4, -

$SC(R^{3b})(N(R^4)(R^4))$, $-N(R^4)C(R^{3b})R^4$, $-N(R^4)C(R^{3b})OR^4$, $-N(R^4)C(R^{3b})(N(R^4)(R^4))$, W^3 or $-R^5W^3$;

R^{3d} is $-C(R^{3b})R^4$, $-C(R^{3b})OR^4$, $-C(R^{3b})W^3$, $-C(R^{3b})OW^3$ or $-C(R^{3b})(N(R^4)(R^4))$;

R^4 is -H, or an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2 to 18 carbon atoms;

W^3 is W^4 or W^5;

W^4 is R^6, $-C(R^{3b})R^6$, $-C(R^{3b})W^5$, $-SO_{M2}R^6$, or $-SO_{M2}W^5$, wherein R^6 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

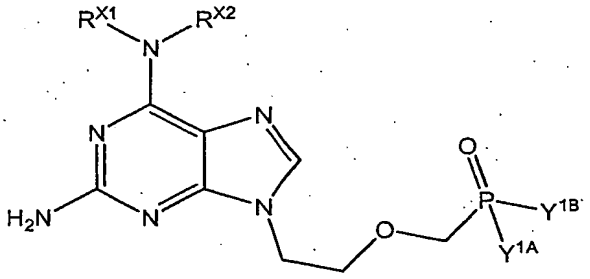
W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups; and

M2 is 0, 1 or 2;

and pharmaceutically acceptable salts thereof.

ABSTRACT OF THE DISCLOSURE

Compounds and compositions of Formula I are described, useful as anti-proliferative agents, and in particular anti-HPV,



I

wherein:

Y^{1A} and Y^{1B} are independently Y^1;

R^{X1} and R^{X2} are independently R^X;

Y^1 is =O, -O(R^X), =S, -N(R^X), -N(O)(R^X), -N(OR^X), -N(O)(OR^X), or -N(N(R^X)(R^X));

R^X is independently R^1, R^2, R^4, W^3, or a protecting group;

R^1 is independently -H or alkyl of 1 to 18 carbon atoms;

R^2 is independently R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is -H, -F, -Cl, -Br, -I, $-CF_3$, -CN, N_3, $-NO_2$, or $-OR^4$;

R^{3b} is =O, -O(R^4), =S, -N(R^4), -N(O)(R^4), -N(OR^4), -N(O)(OR^4), or -N(N(R^4)(R^4));

R^{3c} is $-R^4$, -N(R^4)(R^4), -SR^4, -S(O)R^4, -S(O)$_2R^4$, -S(O)(OR^4), -S(O)$_2$(OR^4), -OC(R^{3b})R^4, -OC(R^{3b})OR^4, -OC(R^{3b})(N(R^4)(R^4)), -SC(R^{3b})R^4, -SC(R^{3b})OR^4, -

$SC(R^{3b})(N(R^4)(R^4))$, $-N(R^4)C(R^{3b})R^4$, $-N(R^4)C(R^{3b})OR^4$, $-N(R^4)C(R^{3b})(N(R^4)(R^4))$, W^3 or $-R^5W^3$;

R^{3d} is $-C(R^{3b})R^4$, $-C(R^{3b})OR^4$, $-C(R^{3b})W^3$, $-C(R^{3b})OW^3$ or $-C(R^{3b})(N(R^4)(R^4))$;

R^4 is -H, or an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2 to 18 carbon atoms;

W^3 is W^4 or W^5;

W^4 is R^6, $-C(R^{3b})R^6$, $-C(R^{3b})W^5$, $-SO_{M2}R^6$, or $-SO_{M2}W^5$, wherein R^6 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups; and

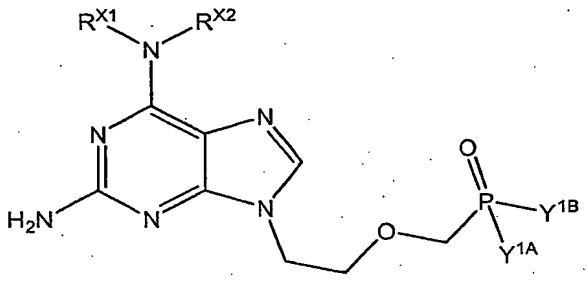
M2 is 0, 1 or 2;

and pharmaceutically acceptable salts thereof.

As such there exists an unmet need for effective HPV treatment. It has now been surprisingly discovered compounds that meet this need, and provide other benefits as well. Relevant background art: Snoeck et al., Antimicrobial Agents and Chemotherapy, vol. 46(11), pp. 3356 – 3361 (Nov. 2002); Keith et al., Antimicrobial Agents and Chemotherapy, vol. 47(7), pp. 2193-2198 (July 2003); Christensen et al., Antiviral Research, vol. 48, pp. 131-142 (2000); U.S. Patent Publication No. 2003/0072814 A1; U.S. Patent 5,798,340; and PCT Application No. PCT/CZ96/00011.

SUMMARY OF THE INVENTION

A compound of formula I,



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wherein:

Y^{1A} and Y^{1B} are independently Y^1;

R^{X1} and R^{X2} are independently R^X;

Y^1 is =O, -O(R^X), =S, -N(R^X), -N(O)(R^X), -N(OR^X), -N(O)(OR^X), or -N(N(R^X)(R^X));

R^X is independently R^1, R^2, R^4, W^3, or a protecting group;

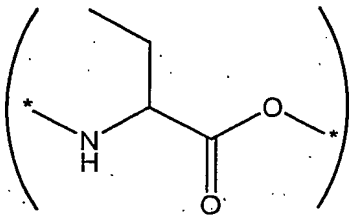
R^1 is independently -H or alkyl of 1 to 18 carbon atoms;

R^2 is independently R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

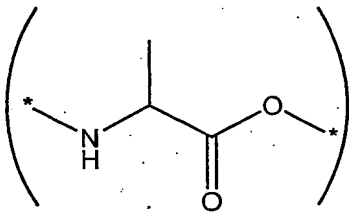
R^{3a} is -H, -F, -Cl, -Br, -I, $-CF_3$, -CN, N_3, $-NO_2$, or $-OR^4$;

R^{3b} is =O, -O(R^4), =S, -N(R^4), -N(O)(R^4), -N(OR^4), -N(O)(OR^4), or -N(N(R^4)(R^4));



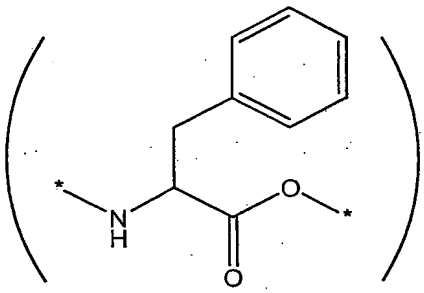
where the points of attachment are designated by the " * ".

As used herein the term "Ala" refers to a divalent moiety of alanine,



where the points of attachment are designated by the " * ".

As used herein the term "Phe" refers to a divalent moiety of phenyl alanine,



where the points of attachment are designated by the " * ".

As used herein the term "POC" refers to the divalent moiety of hydroxymethyl isopropyl carbonate,